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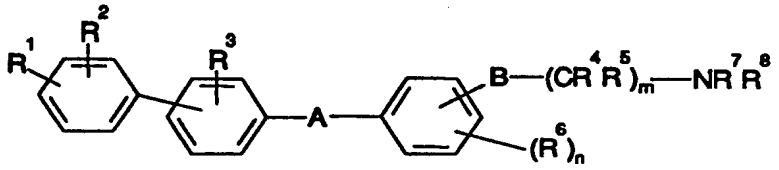
(54) Title: BIPHENYL DERIVATIVES AS 5HT1D ANTAGONISTS

(57) Abstract



(I)

Compounds of formula (I), processes for their preparation and their use as CNS agents are disclosed, in which R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxy C_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_pCO_2R^{11}$, $(CH_2)_pNR^{10}R^{11}$, $(CH_2)_pCONR^{10}R^{11}$, $(CH_2)_pCO_2C_{1-6}$alkyl, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and p is 1 to 3; R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl; R^4 and R^5 are independently hydrogen or C_{1-6}alkyl; R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy; R^7 and R^8 are independently hydrogen, C_{1-6}alkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5-7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur; A is CONH or NHCO; B is oxygen, $S(O)_p$ where p is 0, 1 or 2, or B is NR^{12} where R^{12} is hydrogen or C_{1-6}alkyl; m is 2 to 4; and n is 1 or 2.

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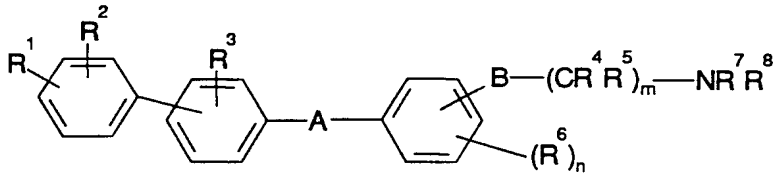
BIPHENYL DERIVATIVES AS 5HT1D ANTAGONISTS

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders.

A structurally distinct class of compounds have now been discovered and have been found to exhibit $5HT_{1D}$ antagonist activity. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



(I)

in which

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_pCO_2R^{11}$, $(CH_2)_pNR^{10}R^{11}$, $(CH_2)_pCONR^{10}R^{11}$, $(CH_2)_pCO_2C_{1-6}$alkyl, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and p is 1 to 3;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^7 and R^8 are independently hydrogen, C_{1-6}alkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5-7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur;

A is CONH or NHCO;

B is oxygen, $S(O)_p$ where p is 0, 1 or 2, NR^{12} where R^{12} is hydrogen, C_{1-6}alkyl or phenylC_{1-6}alkyl, or B is $CR^4{=}CR^5$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

m is 1 to 4; and
n is 1 or 2.

C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_pCO_2R^{11}$, $(CH_2)_pNR^{10}R^{11}$, $(CH_2)_pCONR^{10}R^{11}$, $(CH_2)_pCO_2C_{1-6}$alkyl, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and p is 1 to 3.

Suitably R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl. Preferably R^2 is C_{1-6}alkyl, in particular methyl. Preferably R^3 is hydrogen.

Suitably R^4 and R^5 are independently hydrogen or C_{1-6}alkyl.

Suitably R^7 and R^8 are independently hydrogen or C_{1-6}alkyl. Examples of R^7 and R^8 heterocyclic rings include morpholine, piperazine and piperidine. Optional substituents for such rings include C_{1-6}alkyl. Preferably R^7 and R^8 are both C_{1-6}alkyl, in particular methyl.

Suitably R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy. Preferably R^6 is C_{1-6}alkoxy such as methoxy.

Suitably A is CONH or NHCO. Preferably A is CONH.

Suitably B is oxygen, $S(O)_p$ where p is 0, 1 or 2, NR^{12} where R^{12} is hydrogen, C_{1-6}alkyl or phenylC_{1-6}alkyl, or B is $CR^4{=}CR^5$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl. Preferably B is oxygen.

Suitably m is 1 to 4, preferably m is 1 or 2

Suitably n is 1 or 2, preferably n is 1.

The groups $-B(CR^4R^5)_mNR^7R^8$ and R^6 can be attached to the phenyl ring at any suitable position. Preferably the group $-B(CR^4R^5)_mNR^7R^8$ is meta to the amide linkage and the group R^6 is para to the amide linkage. The groups R^1, R^2 and R^3 can be attached at any suitable position.

Particularly preferred compounds of the invention include:

N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-methoxycarbonyl-2'-methylbiphenyl-4-carboxamide,

N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-N-

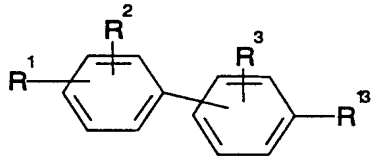
methylcarboxamidobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-N, N-dimethylcarboxamidobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-carboxamidobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-cyanobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-acetyl-2'-methylbiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(methoxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(hydroxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide,
or a pharmaceutically acceptable salt thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the invention.

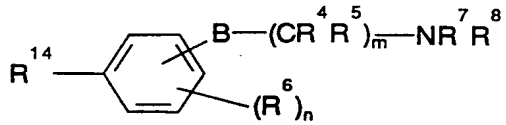
In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) reaction of a compound of formula (II):



(II)

with a compound of formula (III):



(III)

wherein B, m, n, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I) and R^{13} and R^{14} contain the appropriate functional group(s) necessary to form the A moiety; and optionally thereafter in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

Suitably one of R^{13} or R^{14} is an activated carboxylic acid derivative, such as an acyl halide or acid anhydride, and the other is an amine group. Activated compounds of formulae (II) or (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazole. Preferably R^{13} or R^{14} is a group COL where L is halo, particularly chloro.

A compound of formulae (II) and (III) are typically reacted together in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, triethylamine or pyridine.

Intermediate compounds of formulae (II) and (III) are commercially available or can be prepared using standard procedures such as those outlined in EPA 533266/7/8. Certain intermediate compounds of formulae (II) and (III) are novel and form a further aspect of the invention.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

Certain compounds of formula (I) can be converted into further compounds of formula (I). For example compounds in which R^7 and R^8 are both hydrogen or one of R^7 or R^8 is hydrogen and the other is C_{1-6}alkyl can be converted to compounds in which R^7 and R^8 are both C_{1-6}alkyl using standard alkylation techniques.

$5HT_{1D}$ Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include

Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

$5HT_{1D}$ Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to

methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Description 1
2-(Dimethylaminoethoxy)-4-nitroanisole

A stirred solution of 2-methoxy-5-nitrophenol (5.0g, 0.029 mole) and potassium carbonate (8.3g, 0.060 mole) in acetone (200 ml) and water (60 ml) was treated with N,N-dimethylaminoethyl chloride hydrochloride (8.64g, 0.060 mole) and heated under reflux for 10 h. The mixture was concentrated under vacuum to approx. 80 ml volume, then acidified with 2M HCl acid (150 ml) and washed with ethyl acetate (2 x 80 ml). The acid solution was basified with K_2CO_3 and extracted with ethyl acetate (2 x 100 ml). The combined extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a yellow solid (4.87g, 70%).

^{1}H NMR (250 MHz) $CDCl_3$
δ : 7.92 (1H, dd), 7.77 (1H, d), 6.91 (1H, d), 4.18 (2H, t), 3.96 (3H, s), 2.82 (2H, t), 2.37 (6H, s).

Description 2
2-(Dimethylaminoethoxy)-4-methoxyaniline

A solution of 2-(dimethylaminoethoxy)-4-nitroanisole (D1, 4.8g, 0.020 mole) in ethanol (200 ml) was hydrogenated over 10% Pd-C (0.5g) at room temperature and pressure. When reduction was complete (1h), the catalyst was removed by filtration through kieselguhr and the filtrate concentrated under vacuum to afford the title compound as a pink solid (4.0g, 95%).

^{1}H NMR (250 MHz) $CDCl_3$
δ : 6.71 (1H, d), 6.33 (1H, d), 6.24 (1H, dd), 4.07 (2H, t), 3.78 (3H, s), 3.46 (2H, br s), 2.76 (2H, t), 2.33 (6H, s)

Description 3
4'-Methoxycarbonyl-2'-methylbiphenyl-4-carboxylic acid

A stirred solution of methyl 4-bromo-3-methylbenzoate (EP 0533268 A1) (1.0g, 0.0044 mole) in dry DMF (10ml) under argon was treated with 4-boronobenzoic acid (0.73g, 0.0044 mole) and tetrakis (triphenylphosphine)palladium(0) (80mg), followed by triethylamine (1.8ml, 0.016 mole). The mixture was heated at 100°C for 18 hours, then concentrated *in vacuo*. The residue was treated with ethyl acetate and extracted with 10% $NaHCO_3$ solution. The basic extract was acidified with dil. HCl and extracted with ethyl

acetate. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a white solid (0.46g, 39%).

^1H NMR (250MHz, d^6DMSO)
δ(ppm): 13.1 (brs, 1H), 8.04 (d, 2H), 7.93 (s, 1H), 7.87 (d, 1H), 7.51 (d, 2H), 7.38 (d,1H), 3.87 (s, 3H), 2.30 (s, 3H)

Description 4
4'-Carboxamido-2'-methylbiphenyl-4-carboxylic acid

4-Bromo-3-methylbenzamide (0.369g, 1.725mmole) was suspended in 1,2-dimethoxyethane (20ml) and was treated with 4-carboxyphenylboronic acid (0.286g, 1.725mmole), followed by a solution of sodium carbonate (0.823g, 7.76mmole) in water (20ml). The mixture was flushed with argon and tetrakistriphenylphosphinepalladium (0) (0.040g) was added. The reaction mixture was then heated to reflux with stirring. After 24h, the 1,2-dimethoxyethane was removed by evaporation under reduced pressure and the aqueous residue was extracted with ethyl acetate. The aqueous layer was then acidified to pH1 and the resultant solid was filtered off and was dried *in vacuo* to give the title compound as a white solid (0.393g, 89%).

^1H NMR (250MHz, d^6DMSO)
δ(ppm): 13.0 (brs, 1H), 8.02 (d, 3H), 7.82 (s, 1H), 7.78 (d, 1H), 7.52 (d, 2H), 7.38 (s, 1H), 7.28 (d, 1H), 2.38 (s, 3H)

Description 5
N-Methyl-4'-carboxamido-2'-methylbiphenyl-4-carboxylic acid

Using the method outlined in Description 4, N-methyl-4-bromo-3-methylbenzamide (0.363g, 1.59mmole) was converted to the title compound as a white solid (0.338g, 79%)

^1H NMR (250MHz, d^6DMSO)
δ(ppm): 8.52 (dd, 1H), 8.02 (d, 2H), 7.80 (s, 1H), 7.75 (d, 1H), 7.50 (d, 2H), 7.30 (d, 1H), 2.80 (d, 3H), 2.30 (s, 3H)

Description 6
N, N-Dimethyl-4'-carboxamido-2'-methylbiphenyl-4-carboxylic acid

Using the method outlined in Description 4, N, N-dimethyl-4-bromo-3-methylbenzamide (0.383g, 1.583mmole) was converted to the title compound as a white solid (0,354g, 79%)

^{1}H NMR (250MHz, d^{6}DMSO)
δ(ppm): 8.02 (d, 2H), 7.52 (d, 2H), 7.38 (s, 1H), 7.29 (s, 2H), 3.00 (s, 6H), 2.30 (s, 3H)

Description 7
N-Methoxy-N-methyl-4-bromo-3-methylbenzamide

A stirred suspension of 4-bromo-3-methylbenzoic acid (5.0g, 0.023mole) in thionyl chloride (20ml) was heated under reflux for 2 hours, then concentrated *in vacuo*. The residual acid chloride was dissolved in dichloromethane (100ml) and added dropwise over 10 minutes to a stirred solution of N,O-dimethylhydroxylamine hydrochloride (2.4g, 0.025mole) and pyridine (5.6ml, 0.069mole) in dichloromethane (150ml) and acetonitrile (20ml) at -20°C. The reaction mixture was allowed to warm to room temperature over 3 hours then treated with 10% Na_2CO_3 solution and extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a pale yellow oil (5.9g, 100%).

^{1}H NMR (200MHz, $CDCl_3$)
δ (ppm):7.60-7.50 (m, 2H), 7.37 (dd, 1H), 3.54 (s, 3H), 3.35 (s, 3H), 2.42 (s, 3H)

Description 8
4-Bromo-3-methylacetophenone

A solution of N-methoxy-N-methyl-4-bromo-3-methylbenzamide (D7) (1.50g, 0.0057mole) in dry ether (30ml) was added dropwise over 10 minutes to a stirred solution of methylmagnesium iodide (0.0075mole) in dry ether (15ml) under argon. The mixture was then heated under reflux for 1 hour, allowed to cool and poured into well stirred 1M HCl (50ml). The mixture was extracted with ethyl acetate and the extract washed with 10% Na_2CO_3 solution, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a pale yellow oil (1.14g, 94%).

^{1}H NMR (250MHz, $CDCl_3$)

δ (ppm):7.81 (s, 1H), 7.62 (s, 2H), 2.57 (s, 3H), 2.45 (s, 3H)

Description 9

4'-Acetyl-2'-methylbiphenyl-4-carboxylic acid

The title compound was prepared from 4-bromo-3-methylacetophenone (D8) using a procedure similar to Description 4 (80%).

^{1}H NMR (250MHz, $CDCl_3$)

δ (ppm):8.13 (d, 2H), 7.88 (d, 1H), 7.84 (d, 1H), 7.40 (d, 2H), 7.34 (d, 1H), 2.65 (s, 3H), 2.34 (s, 3H)

Example 1

N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-cyanobiphenyl-4-carboxamide

The product from Description 4 (0.100g, 0.392mmole) was suspended in thionyl chloride (7ml) and heated to reflux. After 0.5h, the reaction mixture was allowed to cool and was evaporated under reduced pressure. The yellow oily residue was then azeotroped with toluene (1×10ml) and was dried *in vacuo* to give the crude acid chloride as a yellow solid. The product from Description 2 was dissolved in dry THF (2ml), a solution of sodium hydroxide (0.048g, 1.18mmole) in water (2ml) was added and to this stirred mixture was added the crude acid chloride in THF (2ml). The mixture was then stirred at room temperature for 2h before being partitioned between CH_2Cl_2 and water. The aqueous layer was then extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a buff solid. This was purified by preparative T.L.C. using 10% MeOH/CH_2Cl_2 as eluant to give the title compound as a colourless oil (0.046g, 27%) which was converted to its oxalate salt mp 207-208°C

^{1}H NMR (270MHz, d^6DMSO)

δ(ppm): 10.30 (s, 1H), 8.04 (d, 2H), 7.88 (s, 1H), 7.78 (d, 1H), 7.62 (s, 1H), 7.54 (d, 2H), 7.44 (d, 1H), 7.39 (d, 1H), 7.00 (d, 1H), 4.28 (t, 2H), 3.89 (s, 3H), 3.42 (t, 2H), 2.84 (s, 6H), 2.32 (s, 3H)

Example 2

N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-methoxycarbonyl-2'-methylbiphenyl-4-carboxamide

The title compound was prepared from 4'-methoxycarbonyl-2'-methylbiphenyl-4-carboxylic acid (D3) and 2-(dimethylaminoethoxy)-4-methoxyaniline (D2) using a similar procedure to Example 1 as a white solid (13%) mp 131-133°C.

^{1}H NMR (250MHz, $CDCl_3$)
δ(ppm): 8.3 (brs, 1H), 8.03-7.87 (m, 4H), 7.51 (d, 1H), 7.40 (d, 2H), 7.28 (d, 1H), 7.11 (dd, 1H), 6.84 (d, 1H), 4.12 (t, 2H), 3.94 (s, 3H), 3.84 (s,3H), 2.78 (t, 2H), 2.30 (s, 9H).

Example 3

N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-N-methylcarboxamidobiphenyl-4-carboxamide

The product from Description 5 (0.170g, 0.632mmole) was suspended in dichloromethane (10ml) and treated with oxalyl chloride (0.083ml, 0.948mmole) followed by a drop of dry DMF. The mixture was then stirred at room temperature for 16h, before being evaporated under reduced pressure and dried *in vacuo*. The resulting pale yellow solid was then redissolved in dichloromethane (5ml) and added to a stirred solution of the product from Description 2 (0.126g, 0.600mmole) in dichloromethane (10ml) containing triethylamine (0.083ml, 0.600mmole). The reaction mixture was then stirred at room temperature overnight before being washed with sodium bicarbonate solution. The organic layer was then dried (Na_2SO_4) and was evaporated under reduced pressure to give a brown oil, which was purified by silica-gel chromatography (10% MeOH/CH_2Cl_2 as eluant) to give the title compound as a pale yellow oil (0.066g, 23%) which was converted to its oxalate salt mp 208-210°C

^{1}H NMR free base (250MHz, $CDCl_3$)
δ(ppm): 8.03 (s, 1H), 7.92 (d, 2H), 7.71 (s, 1H), 7.62 (d, 1H), 7.51 (s, 1H), 7.39 (d, 2H), 7.21 (s, 1H), 7.11 (dd, 1H), 6.88 (d, 1H), 6.29 (q, 1H), 4.20 (t, 2H), 3.83 (s, 3H), 3.08 (d, 3H), 2.82 (t, 2H), 2.40 (s, 6H), 2.30 (s, 3H)

Example 4
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-N, N-dimethylcarboxamidobiphenyl-4-carboxamide

Following the method outlined in Example 3, the product from description 6 (0.150g, 0.530mmole) was transformed into the title compound (0.097g) which was converted to its oxalate salt mp 181-183°C

^{1}H NMR free base (250MHz, $CDCl_3$)
δ(ppm): 8.41 (s, 1H), 7.97 (d, 2H), 7.58 (s, 1H), 7.38 (s, 1H), 7.32-7.14 (m, 5H), 6.87 (d, 1H), 4.30 (t, 2H), 3.89 (s, 3H), 3.18 (s, 3H), 3.04 (s, 3H), 2.84 (t, 2H), 2.41 (s, 6H), 2.32 (s, 3H)

Example 5
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-carboxamidobiphenyl-4-carboxamide

The product from Description 4 (0.113g, 0.551mmole), and the product from Description 2 (0.116g, 0.551mmole) were dissolved together in dry DMF (5ml) and EDC.HCl (0.111g, 0.57mmole) was added. The mixture was then stirred at room temperature. After 16h, the reaction mixture was evaporated under reduced pressure to give a brown oil. Water (20ml) was added and the resultant solid filtered off and dried *in vacuo*, before being recrystallised from methanol to give the title compound as an off white solid (0.013g, 5%) mp 212-213°C

^{1}H NMR (270MHz, d^6DMSO)
δ(ppm): 10.18 (s, 1H), 8.04 (d, 3H), 7.90 (s, 1H), 7.78 (d, 1H), 7.52 (d, 3H), 7.33 (m, 3H), 6.95 (d, 1H), 4.04 (t, 2H), 3.79 (s, 3H), 2.64 (t, 2H), 2.30 (s, 3H), 2.20 (s, 6H)

Example 6
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-acetyl-2'-methylbiphenyl-4-carboxamide

The title compound was prepared from 4'-acetyl-2'-methylbiphenyl-4-carboxylic acid (D9) followed a similar procedure to Example 3 (60%) mp 129-130°C.

^{1}H NMR (250MHz, $CDCl_3$)

δ (ppm): 8.00-7.82 (m, 5H), 7.48 (d, 1H), 7.43 (d, 2H), 7.32 (d, 1H), 7.08 (dd, 1H), 6.86 (d, 1H), 4.16 (t, 2H), 3.85 (s, 3H), 2.80 (t, 2H), 2.65 (s, 3H), 2.34 (s, 6H), 2.33 (s, 3H)

Example 7

N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(methoxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide

Methoxylamine hydrochloride (45mg, 0.54 mmole) was added to a stirred solution of potassium t-butoxide (45mg, 0.40mmole) in methanol (5ml) under argon. After 20 minutes at room temperature, the solution was treated with a solution of N-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-4'-actyl-2'-methylbiphenyl-4-carboxamide (E6, 120mg, 0.27 mmole) in methanol (3ml) and stirred at room temperature for 18 hours, followed by 1 hour heating under reflux. The solution was allowed to cool, treated with 10% Na_2CO_3 solution (40ml) and extracted with ethyl acetate. The extract was dried (Na_2SO_4), concentrated *in vacuo* and the residue recrystallised from ethyl acetate /60-80 petrol to afford the title compound as a white solid (38mg, 30%) mp 165-167°C.

^1H NMR (250MHz, $CDCl_3$)
δ (ppm): 7.98 (s, 1H), 7.92 (d, 2H), 7.59 (d, 1H), 7.56-7.47 (m, 2H), 7.41 (d, 2H), 7.26 (d, 1H), 7.08 (dd, 1H), 6.84 (d, 1H), 4.14 (t, 2H), 4.02 (s, 3H), 3.85 (s, 3H), 2.79 (t, 2H), 2.32 (s, 6H), 2.30 (s, 3H), 2.26 (s, 3H)

Example 8

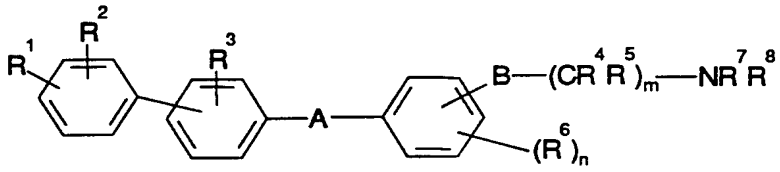
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(hydroxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide

The title compound was prepared from hydroxylamine hydrochloride and N-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-4'-acetyl-2'-methylbiphenyl-4-carboxamide (E6) using a similar procedure to Example 7 (34%) mp 219-220°C

^1H NMR (200MHz, d^6 DMSO)
δ (ppm): 11.25 (s, 1H), 10.15 (s, 1H), 8.03 (d, 2H), 7.65-7.47 (m, 5H), 7.37 (dd, 1H), 7.27 (d, 1H), 6.95 (d, 1H), 4.13 (t, 2H), 3.75 (s, 3H), 2.66 (t, 2H), 2.30 (s, 3H), 2.23 (s, 6H), 2.19 (s, 3H)

CLAIMS:

1. A compound of formula (I) or a salt thereof:



(I)

in which

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_pCO_2R^{11}$, $(CH_2)_pNR^{10}R^{11}$, $(CH_2)_pCONR^{10}R^{11}$, $(CH_2)_pCO_2C_{1-6}$alkyl, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and p is 1 to 3;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^7 and R^8 are independently hydrogen, C_{1-6}alkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5-7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur;

A is CONH or NHCO;

B is oxygen, $S(O)_p$ where p is 0, 1 or 2, NR^{12} where R^{12} is hydrogen, C_{1-6}alkyl or phenylC_{1-6}alkyl, or B is $CR^4=CR^5$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

m is 1 to 4; and

n is 1 or 2.

2. A compound according to claim 1 in which R^1 is cyano, acyl, CO_2R^{10}, $CONR^{10}R^{11}$ or $CR^{10}=NOR^{11}$.

3. A compound according to claim 2 or 3 in which R^2 is C_{1-6}alkyl.

4. A compound according to any one of claims 1 to 3 in which R^3 is hydrogen

5. A compound according to any one of claims 1 to 4 in which B is oxygen.

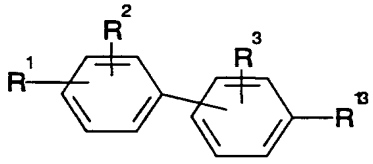
6. A compound according to any one of claims 1 to 5 in which m is 1 or 2 and R^4 and R^5 are both C_{1-6}alkyl.

7. A compound according to claim 1 which is:
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-methoxycarbonyl-2'-methylbiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-N-methylcarboxamidobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-N, N-dimethylcarboxamidobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-carboxamidobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-cyanobiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-acetyl-2'-methylbiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(methoxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(hydroxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide,
or a pharmaceutically acceptable salt thereof.

8. A process for the preparation of a compound of formula (I) which comprises

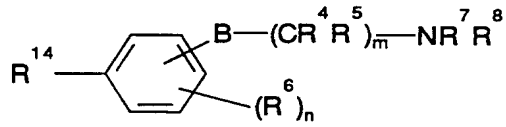
(a) reaction of a compound of formula (II):

(a) reaction of a compound of formula (II):



(II)

with a compound of formula (III):



(III)

wherein B, m, n, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I) and R^{13}

and R^{14} contain the appropriate functional group(s) necessary to form the A moiety; and optionally thereafter in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

9. A compound according to any one of claims 1 to 7 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/EP 95/00900

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C233/75 C07C235/84 C07C251/48 C07C255/57 A61K31/165 A61K31/275

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 533 266 (GLAXO) 24 March 1993 cited in the application see page 4, line 47 - page 5, line 34; claims; examples	1-10
P,Y	GB,A,2 276 161 (GLAXO) 21 September 1994 see whole document	1-10
A	EP,A,0 496 378 (DR. KARL THOMAE GMBH) 29 July 1992 see claims; examples	1-10
A	US,A,4 038 416 (MORI ET. AL.) 26 July 1977 see claims; examples	1-10
A	CH,A,622 005 (CHUGAI SEIYAKU KABUSHIKI KAISHA) 13 March 1981 see claims; examples	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 1995	-7. 06. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Helps, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/EP 95/00900

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		JP-A-	6107649	19-04-94
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		JP-A-	52027742	02-03-77
		CA-A-	1055495	29-05-79
		NL-A-	7609208	22-02-77
		SE-A-	7511454	15-04-76